REMARKS

Upon entry of this amendment, claims 1, 4-19 and 38-40 are pending. Claims 1, 7-12, and 38 are amended and claims 2-3 and 20-37 are cancelled. Claim 1 is amended to clarify the patient population for reducing oral mucositis and is supported, for example, at lines 20-33 on page 23 of the specification.

Examiner Interview

On October 20, 2009, Examiners Shirley Gembeh and Robert Hayes had a telephonic interview with inventor Kathleen C. Campbell and attorneys for Applicants, Janet S. Hendrickson and John Roedel. The Examiners and the Applicants' representatives discussed the outstanding rejections. In particular, Examiner Hayes suggested claim amendments similar to those made herein and indicated these amendments would overcome the 35 U.S.C. § 102 rejections. Applicants found the suggested amendments acceptable in principle, subject to evaluation of the exact language thereof.

However, no agreement was reached regarding the 35 U.S.C. § 103 or obviousness-type double patenting rejections. Therefore, applicants have expanded these arguments in the response below.

35 U.S.C. § 102 Rejection

Reconsideration is respectfully requested of the rejection of claims 1, 6-15, and 17-19 as anticipated by Hammes et al. (US 3,652,290) under 35 U.S.C. § 102(b). Claim 1 is directed to a method for reducing oral mucositis in a human or animal cancer patient undergoing radiation therapy. The method comprises administering to the patient an effective amount of a protective agent selected from the group consisting of D-methionine, L-methionine, a mixture of D-methionine and L-methionine, and a pharmaceutically acceptable salt thereof. Without conceding merit in the rejection but to advance prosecution, claim 1 has been amended to require the patient be suffering from cancer and undergoing radiation therapy. Hammes discloses a beverage fortified by stabilized Vitamin C wherein the Vitamin C is stabilized by histidine, glycine, or methionine. Hammes does not disclose providing such a beverage to cancer patients undergoing radiation therapy. Thus, Hammes does not anticipate claims 1, 6-15, and 17-19 under 35 U.S.C. § 102(b).

35 U.S.C. § 103 Rejection

Reconsideration is respectfully requested of the rejection of claims 1, 4-9, 10-19, and 26-32 as unpatentable over U.S. Patent No. 6,187,817 (Campbell) in view of U.S. Patent No. 4,961,926 (Gabrilove) and further in view of WO 03/045334 (Kil et al.) under 35 U.S.C. § 103(a). Claim 1 is described in detail in connection with the § 102 rejection. The July 9, 2009 Office action asserts that the only required element of claim 1 is that methionine is administered. However, amended claim 1 requires administration of methionine to a cancer patient undergoing radiation therapy.

The Campbell '817 reference describes methods for preventing or reducing ototoxicity, methods of preventing or reducing weight loss, methods of preventing or reducing gastrointestinal toxicity, methods of preventing or reducing neurotoxicity, and methods of preventing or reducing alopecia wherein all of these conditions arise from treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound. As the Office further admits, the Campbell patent makes no mention of oral mucositis resulting from any type of insult; and the patent provides no reason why D-methionine, L-methionine, or D,L-methionine (hereinafter "methionine") would have any value in dealing with oral mucositis resulting from radiation therapy.

Gabrilove discloses methods of preventing mucositis comprising administering granulocyte colony stimulating factor (GCSF) or a polypeptide analog thereof. In particular, the GCSF analog may be a nonglycosylated polypeptide having an amino acid sequence identical to the sequence of the polypeptide component of naturally occurring GCSF (GCSF contains at least 144 amino acids) except for the presence of an additional methionine at the N-terminus. In one embodiment described in the Gabrilove reference, this 20,000 Dalton protein has one additional methionine residue to give a total of 145 amino acids. In contrast, the protectant agent claimed in claims 1 and 20 is D-methionine, L-methionine, and a mixture of D-methionine and L-methionine.

Kil et al. teach combinations of chemoprotectants that ameliorate at least one side effect of chemotherapy. The chemoprotectants disclosed include methionine, N-acetyl-DL-methionine, S-adenosylmethionine, cysteine, homocysteine, cystathione, cysteamine, N-acetylcysteine, glutathione, glutathione ethylester, glutathione diethylester, glutathione triethylester, cysteamine, DiNAC, RibCys, RibCyst, β-LactCys, α-LactCys, MeliCys, MaltCys, CellCys, OTCA,

allopurinol, 1-methylallopurinol, 2-methylallopurinol, 5-methylallopurinol, 7-methylallopurinol, 1,5-dimethylallopurinol, 2,5-dimethylallopurinol, 1, 7-dimethylallopurinol, 2,7-dimethylallopurinol, 5,7-dimethylallopurinol, 2,5, 7-trimethylallopurinol, 1-ethoxycarbonylallopurinol, 1-ethoxycarbonyl-5-methylallopurinol, 2-phenyl-1, 2-benzoisoselenazol-3 (2H) -one, and 6-diSeCD.

The chemotherapeutic agents that Kil et al. protect against are carboplatin, oxyplatin, vinblastine, doxorubicin, bleomycin, paclitaxel, cyclophosphamide, adriamycin, altretamine, methotrexate, and fluorouracil wherein the chemotherapeutic agents containing platinum (e.g., cisplatin, carboplatin, and oxyplatin) are the preferred chemotherapeutic agents. However, like the Campbell patent, Kil et al. makes no mention of oral mucositis resulting from any type of insult; and provides no reason why D-methionine, L-methionine, or D,L-methionine would have any value in dealing with oral mucositis resulting from radiation exposure.

Contrary to the assertion in the Office action, amended claim 1 requires more than administration of the drug methionine. As discussed and agreed in the interview, the limitation of the claim to treatment of patients undergoing radiation therapy is a positive concrete limitation of the claim that cannot be ignored in evaluating novelty under §102or obviousness under §103(a). Since the patient population treated by claim 1 is cancer patients undergoing radiation therapy, the issue is whether it would have been obvious to treat oral mucositis arising from radiation therapy in cancer patients by administration of methionine. There can be no basis for inherency in the Campbell '817 patent which does not describe treatment of patients undergoing radiation therapy and does not include any working examples in which the subjects of treatment with cisplatin were also treated with radiation. It matters not that a patient treated according to the method of Campbell for gastrointestinal toxicity from a platinum co-ordination compound might also be treated with radiation. There is no evidence in the prior art of any such treatment, and thus no basis for a novelty rejection under §102(b).

While it is now known that treatment of a patient under chemotherapy with methionine would inherently ameliorate oral mucositis arising from radiation, such inherency was unrecognized in the art, is placed in possession of the art only by the instant application, and thus is not a basis for establishing obviousness under §103(a). There can be no basis for obviousness where the prior art further fails to recognize the potential effect of the treating agent against the condition specified in the claim. As the C.C.P.A has stated in reversing an obviousness rejection

of a claim to a method of treating a specified condition with a defined treatment agent based on the inherent effect of treating a different condition with a similar agent.

> [Inherency] is quite immaterial if, as the record establishes here, one of ordinary skill in the art would not appreciate or recognize that inherent result, *in re Shetty.*[1]

The method claims at issue in *Shetty* were directed to methods for appetite control and the cited prior art disclosed compounds and dosages useful for combating microbial infestation. The *Shetty* court stated that the Office had "failed to show a reasonable expectation, or some predictability" that the prior art compound disclosed in the first reference would be an effective appetite suppressant if administered in the dosage disclosed in the second reference and that the Office's hindsight assertion that the dosages would make the weight loss method obvious was insufficient.[2] Similar to *Shetty*, claim 1 recites a method for reducing oral mucositis in a cancer patient undergoing radiation therapy by administering methionine to said patient while the reference cited against these claims discloses methods for preventing or reducing ototoxicity, methods of preventing or reducing weight loss, methods of preventing or reducing gastrointestinal toxicity, methods of preventing or reducing neurotoxicity, and methods of preventing or reducing alopecia in patients, but only in patients undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound.

Contrary to the Office's assertion that "one skilled in the art would reasonably treat oral mucositis with the same active agent used in treating gastrointestinal toxicity,"[3] oral mucositis and gastrointestinal toxicity are not necessarily coextensive. While oral mucositis is sometimes broadly classified as a form of gastrointestinal toxicity, oral mucositis is an effect distinctly separate from the effects ordinarily contemplated by "gastrointestinal toxicity" such as nausea, diarrhea and abdominal pain, and generally results from different pathological mechanisms. It is a subtype entirely different from the subtypes to which the references are principally directed. Further, the material difference between oral mucositis and gastrointestinal toxicity is illustrated by Rappoport et al., of record. Not only are the methods for scoring oral mucositis separate and vastly different from those used for gastrointestinal toxicity, but, even more significantly, the authors *found no association or correlation* between the measures for gastrointestinal toxicity and those for oral mucositis. Also, Campbell discloses only administration of anti-tumor

[1] 195 U.S.P.Q. 753.
[2] See id. at 756.
[3] Office action dated July 9, 2009 at page 4.

platinum coordination compounds and does not discuss radiation therapy; as discussed below the mechanistic differences of those insults would not have led a skilled person to reasonably expect that an agent beneficial for ameliorating one toxicity would also be beneficial for ameliorating a completely different toxicity from a different insult.

Further, even though Gabrilove and Campbell are directed to reducing toxicity from chemotherapy, there is no reason to substitute the Campbell's D-methionine, L-methionine, or D,L-methionine into the method of Gabrilove for treating mucositis, and there is manifestly no basis for combining their teachings when Gabrilove treats such toxicity with a 20,000 Dalton protein having 145 amino acids and Campbell uses monomeric D-methionine, L-methionine, or D,L-methionine having a molecular weight of 150 Dalton.

The Office action states that oral mucositis is a well known result of chemotherapy and radiotherapy, but there is no suggestion in the references, or otherwise in the art, that treatment effective against one source of this condition would be effective against an entirely different source. Thus, there was no reason to attempt substitution of the Campbell treatment agent for that of Gabrilove, much less any basis for expectation of success. Nowhere in the art is there any suggestion that the mechanism by which oral mucositis is induced might be the same for both chemotherapy and radiation, and given the vast differences between these treatments and how they function within patient's system, a skilled medical researcher would not have looked to Campbell as a source of learning for treatment of the condition to which Gabrilove is addressed.

Although Elting is cited to support the argument that oral mucositis is a symptom of "gastrointestinal toxicity," Elting is directed to investigating the factors associated with development of viridans streptococcal septicemia in patients undergoing antineoplastic therapy and in Table 3 details oral mucositis, gastritis and/or vomiting, and diarrhea as separate factors predisposing a patient to the development of viridans streptococcal septicemia. Table 3 also shows oral mucositis, gastritis and/or vomiting, and diarrhea have different odds ratios of 4.3, 6.3, and 5.5, respectively. In any case, Elting does not show that one skilled in the art would read Campbell '817 as relating to any condition beyond the abdominal symptoms ordinarily associated with "gastrointestinal toxicity."

More significantly, even if one skilled in the art were to read Campbell's "gastrointestinal toxicity" as including oral mucositis, Elting contains no suggestion that oral mucositis arising from radiation would result from the same pathological mechanism which produces oral

mucositis from chemotherapy, much less that any treatment for oral mucositis induced by chemotherapy would or could have any beneficial effect on oral mucositis induced by radiation. Radiation treatment is usually directly targeted to a specific area of the body wherein the diseased tissue is located, whereas chemotherapy operates through more systemic mechanisms. While systemic effects may also be incurred from radiation, mucositis is understood to arise from proximity to diseased tissue. More generally, the pattern of toxicities to tissues from radiation shows that the mechanisms of damage from radiation exposure are different in different tissues and depend on the specific region of exposure to radiation. Thus, since the mechanisms of radiation damage to different tissues are unpredictable, and different from the mechanisms governing the gastrointestinal effects of cisplatin, there was no reasonable basis for expectation that administration of methionine would be beneficial to ameliorate oral mucositis arising from radiation therapy.

The Office asserts that "substituting Gabriloves' compound with Campbell is reasonable since there is an overlap in the disease treatment." The "overlap" to which this refers is unclear to Applicant. There is no overlap between Campbell '817 and Gabrilove. One uses a monomeric amino acid for treatment of gastrointestinal conditions arising from administration of a platinum co-ordination compound while the other uses a polypeptide derived from 145 amino acids for treatment of oral mucositis arising from radiation. There is certainly no overlap between a monomeric amino acid and a 20,000 Dalton polypeptide. If there is any overlap at all, it is between the specific condition of oral mucositis and the genus of "gastrointestinal toxicity," as broadly construed by a particular reference, i.e., Elting, that has nothing to do with radiation therapy. That Campbell '817 and Gabrilove are broadly directed to conditions arising in disparate treatments for a common category of diseases is not a reason to combine them at all, much less a reason to substitute the very different agent Campbell teaches as effective against a condition arising from chemotherapy for the agent which Gabrilove teaches to be effective against a condition arising from radiation. If Campbell and Gabrilove are construed as having a broad common treatment objective, such general objective is the goal of every reference concerned with reducing side effects of chemotherapy and radiation therapy, which provides no

reason to combine these particular references out of the myriad of palliative treatments for such side effects.[4]

There was no motivation in the art to administer methionine to a cancer patient undergoing radiation therapy and in need of treatment for oral mucositis. Although the side effect of oral mucositis in patients receiving radiation treatments for various conditions was known, the art did not suggest a way to alleviate radiation-induced oral mucositis that was in any way comparable to the instantly claimed method. Thus, there was no teaching, motivation or suggestion in the art to try methionine or any amino acid as a treatment for oral mucositis arising from radiation. Further, there was not a reasonable expectation that administration of methionine to a cancer patient undergoing radiation therapy and in need of treatment for oral mucositis would have had a beneficial effect.

Moreover, there is no reason provided why a skilled person would have substituted methionine as disclosed by Kil for the GCSF protein of Gabrilove to treat oral mucositis resulting from radiation exposure. A skilled person would have attributed the anti-mucositis effect of the GCSF protein to the specific structural aspects of the protein and not solely or primarily to the presence of an additional methionine residue at the N-terminus. From the Gabrilove disclosure, a skilled person would have learned that recombinant hG-CSF (rhG-CSF) is "a specific growth and differentiation factor for neutrophil granulocytes"[5] and that "recombinant hG-CSF may reduce the incidence of mucositis by enhancing the number of neutrophils, as well as their functional capability to guard the mucosal barriers more efficiently."[6] From these statements, a skilled person would have known that the primary, secondary, and tertiary structure of the 20,000 Dalton rhG-CSF protein was instrumental in its neutrophil granulocyte growth stimulation and mucositis protection functions.

A skilled person would not have expected D-methionine, L-methionine, or D,L-methionine, a 150 Dalton small molecule amino acid, to provide the same physiological effect as the 20,000 Dalton GCSF protein, regardless of whether an additional methionine unit happens to

---

[4] *Ex parte Meagher*, Appeal no. 2008-3613; Application No. 10/380,898 decided September 22, 2008 at page 15 (describing that combining references for the purpose of "obtaining a conversion coating having good corrosion resistance and good top coat adhesion properties-which are likely goals of virtually every conversion coating composition-do not provide the ordinary coating formulations chemist with a reason to systematically vary" the prior art compositions to arrive at the claimed composition.).

[5] See U.S. Patent No. 4,961,926, column 2, lines 41 to 43.

[6] See U.S. Patent No. 4,961,926, column 7, line 67 to column 8, line 14.

be present at the N-terminus of the protein. Even if it were assumed that an additional methionine at the N-terminus of the GCSF protein is somehow instrumental in imparting significant properties to the protein as a whole, one skilled in the art would scarcely expect that the monomeric amino acid by itself would provide a comparable effect. By way of example, proteins, including GCSF proteins act upon cell components through various chemical and physical interactions. In particular, the primary, secondary, and tertiary (e.g., three dimensional) structure of the protein including surfaces for binding and interacting with various molecules is well known to be essential to the biological function which the protein exhibits. A protein can also undergo various conformational changes upon binding a molecule at a particular binding site. Monomeric methionine does not have the same type of complex three-dimensional structure and would not be expected to stimulate growth of neutrolphil granulocytes. Thus, a person of ordinary skill would not have expected methionine by itself to be an effective agent against oral mucositis based on the Gabrilove disclosure alone or as combined with the Campbell disclosure.

Kil et al. does not remedy the deficiencies of Campbell or Gabrilove. Like the Campbell patent, Kil et al. makes no mention of mucositis resulting from any type of insult; and provides no reason why D-methionine, L-methionine, or D,L-methionine would have any value in dealing with oral mucositis resulting from radiation therapy. Thus, there was no basis in Campbell, Gabrilove or Kil for combining their teachings in any manner, or for selecting either Campbell or Kil as sources of learning for modifying, in this case drastically modifying, the method of Gabrilove. As explained above for the combination of the Campbell patent and Gabrilove, even if Campbell, Gabrilove, and Kil were read together, they would not have provided a reason to combine their respective and disparate teachings, and even if the teachings were combined, the combination would not have led a person of ordinary skill to find the present claims for reducing oral mucositis using the small molecule methionine obvious for at least the same reasons as described above for the Campbell and Gabrilove combination. Further, as described for the Campbell and Gabrilove combination, a person of ordinary skill would not have expected methionine by itself to be an effective agent against oral mucositis based on the combination of Campbell, Gabrilove, and Kil disclosures.

Claims 38-40

Reconsideration is respectfully requested of the rejection of claims 38-40 as unpatentable over U.S. Patent No. 6,187,817 (Campbell) in view of U.S. Patent No. 4,961,926 (Gabrilove) and further in view of WO 03/045334 (Kil et al.) under 35 U.S.C. § 103(a). Claim 38 is dependent on claim 1 and directed to a method of reducing oral mucositis wherein the patient is a cancer patient, is undergoing radiation therapy, and is undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound. Thus, claims 38-40 are patentable over U.S. Patent No. 6,187,817 (Campbell) in view of U.S. Patent No. 4,961,926 (Gabrilove) and further in view of WO 03/045334 (Kil et al.) under 35 U.S.C. § 103(a) for at least the same reasons as claim 1.

Claims 26-32 were cancelled herein, thus the rejection of those claims is moot.

It is respectfully submitted that the Office has failed to establish obviousness based on the cited references or by evidence of the level of skill in the art or the nature of the problem that is not based upon impermissible hindsight reconstruction. Thus, claims 1, 5-19, and 38-40 are patentable over the cited references.

Obviousness-type Double Patenting

Reconsideration of the rejection of claims 20-32 as unpatentable over claims 1, 3-5, and 7-32 of U.S. Application No. 10/694,448, now U.S. Patent No. 7,557,142 and claims 1-36 of U.S. Patent No. 6,187,817. Since claims 20-32 are canceled, these rejections are moot.

Reconsideration of the rejection of claims 1, 4-19, and 38-40 as being unpatentable over claims 1-9, 11-13, 15-25, and 27-33 of U.S. Application No. 10/694,432 is respectfully requested. The analysis employed in an obvious-type double patenting rejection parallels the guidelines of a 35 U.S.C. § 103 obviousness determination.[7] However, an important distinction exists. A rejection for obviousness must be based on a comparison of the claimed invention to the entirety of the disclosure in the prior art reference, whereas an obviousness-type double patenting rejection must be grounded on a comparison of the claimed invention to the claims, **and only the claims**, of the reference.[8]

[7] In re Braat, 937 F.2d 589 (Fed. Cir. 1991).
[8] Purdue Pharma L.P. v. Boehringer Ingelheim GMbH, 98 F.Supp.2d 362, 392, 55 USPQ2d 1168, 1190 (S.D.N.Y. 2000), *aff'd*, 237 F.3d 1359, 57 USPQ2d 1647 (Fed. Cir. 2001).

The '432 application contains claims directed to methods for treating alopecia in a patient experiencing exposure to radiation by administering D-methionine, L-methionine, or a mixture of D- and L-methionine. Since the mechanism for alopecia and oral mucositis arising from radiation therapy are significantly different, none of the claims of the '432 application provides a reason to try methionine for treatment of oral mucositis in a cancer patient undergoing radiation therapy. Also, the '432 claims provide no reason to expect that such administration of D-methionine, L-methionine, or a mixture of D- and L-methionine would have been successful to reduce oral mucositis in a cancer patient undergoing radiation therapy.

CONCLUSION

Applicant submits that the present application is now in a condition for allowance and requests early allowance of the pending claims.

The Commissioner is hereby authorized to charge any under payment or credit any over payment to Deposit Account No. 19-1345.

Respectfully submitted,

Janet S. Hendrickson, Ph.D., Reg. No. 55,258
SENNIGER POWERS LLP
100 North Broadway, 17th Floor
St. Louis, Missouri 63102
(314) 231-5400

JSH/clp